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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/645,794	08/21/2003	Andrew J. Bett	20699Y	8205

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EXAMINER	
HORNING, MICHELLE S	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/645,794	BETT ET AL.	
	Examiner	Art Unit	
	MICHELLE HORNING	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9-11,21-23 and 84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9-11,21-23 and 84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/30/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is responsive to communication filed 4/30/2008. The status of the claims is as follows: claims 1-5, 7, 9-11, 21-23 and 84 are under current examination.

The following rejections are withdrawn due to claim amendments or the finding of additional art:

1. 35 USC 112, 2nd paragraph; and

2. 35 USC 103 (Mehtali et al, Falck-Pedersen and Li); and

3. 35 USC 103 (Mehtali et al, Falck-Pedersen, Li et al and Megede et al).

Response to Arguments

Applicant's arguments filed 4/30/2008 have been fully considered but they are not persuasive. They are addressed individually below.

Applicant submits the following recitation:

Applicants respectfully submit that the Examiner has not provided any reasoning why Lusky does not teach away from the invention and has not provided a reasoning why, in view of Lusky, the combination of Mehtali and Falck-Pedersen is desirable. As previously noted in the March 2007 Amendment, Lusky teaches that multiply deleted adenovirus vectors have clear advantages over E1 only deleted vectors, including (1) prevention of replication-competent adenovirus through recombination events, and (2) an improved safety profile due to the oncogenic potential of the E4 ORF6. See Lusky, pg. 2031, col. 1, last paragraph. Given this teaching, there would be a strong motivation to use the teachings of Falck-Pedersen (producing a virus using a cell line providing the functions of E 1 and E4 either stably integrated in the genome or having one of the functions provided with a helper virus; see Falck-Pedersen, col. 9, lines 29-41) to produce El- E4- adenovirus vectors as the necessary E4 function is provided in trans. In view of the teachings of Lusky, one would not be motivated to provide E4 ORF6 function in cis. Instead, one would have been motivated to create replication-defective adenovirus vectors with minimal E4 regions and strongly consider supplying at least E4ORF6 in *trans*. (REMARKS, page 6).

In response, Lusky et al describe *isogenic* multiply-deleted adenoviral vectors while the instantly claimed invention requires two separate serotypes. Falck-Pedersen provides the following teaching: "Importantly, albeit unexplained, adenoviruses of different groups do not recombine when co-infection of the same host occurs. In contrast, the adenoviruses recombine efficiently within a group (Sambrook et al., J. Mol. Biol., 97, 369-390 (1975)). The failure of adenoviruses to recombine between serogroups highlights the genetic variance of the adenoviral groups" (see paragraph 10, emphasis added). Separately, the author also notes the toxic effects of gene products from the E4 region and describes the use of a regulable promoter so that the gene function of the E4 region is provided only when the replication deficient adenovirus is in need of the toxic products for its replication (see paragraph 42). Thus, Applicant's argument that Lusky et al teaches away from the instant invention is not entirely correct, given Lusky et al teach an isogenic vector, differential serotypes do not recombine and methods of regulating the toxic effects of the E4 gene products are known.

Applicants note that it is unclear how the teachings of Mehtali and Falck-Pedersen should be combined to obtain "optimal results". Falck-Pedersen discloses that the viral yield of an E1-deficient Ad7a virus on 293/ORF6 cells (which provide ORF6 in trans) was essentially the same as that expected for Ad5 infections. See Falck-Pedersen, Example 6 (col. 14, line 20 to col. 15, line 2). One would never expect propagation of a non-group C adenovirus in an Ad5 complementing cell line to be better than propagation of Ad5. Thus, there is no motivation to combine Mehtali and Falck-Pedersen to achieve "optimal" propagation of replication deficient adenoviruses. (REMARKS, page 6).

The argument is not on point. Applicant appears to equate "optimal results" to only viral yields. It was clearly pointed out in the previous office action that Falck-Pedersen described increases in the efficiency of complementation of E1 deficient adenoviruses when the E1 gene products provide are obtained from an adenovirus of a serogroup different from that of the replication deficient adenovirus.

Applicants further submit that there is no reasonable expectation of success for the invention, as reflected in the amended claims. The claims, as amended, require the propagation of a replication-defective adenovirus from subgroup D. Mehtali does not provide any examples of using alternative serotypes, while Falck-Pedersen only exemplifies propagation of Ad7a (subgroup B). There are sufficient sequence differences in the E4 regions of adenoviruses of subgroups B, C, and D (see reference C02, page 456, lines 6-10), that it would be unpredictable whether genetic manipulation in the E4 region of a subgroup D adenovirus would result in a viable adenovirus. Similar results were seen when the E1B region of subgroup B adenoviruses was genetically manipulated. See reference C01, abstract. A critical plX promoter, only present in subgroup B adenoviruses, was inadvertently deleted resulting in vector instability. See id. While the Ad35 genome could be manipulated to retain the plX promoter and provide vector stability, it was unclear at the time of the present invention whether a critical function was present in the E4 region of subgroup D adenoviruses. Such a critical function could prevent the development of E4 adenoviruses from subgroup D. Therefore, Falck-Pedersen's disclosure of a replication-defective Ad7a adenovirus with an intact E4 region does not provide a reasonable expectation of success for an E4- replication-defective adenovirus of subgroup D. (REMARKS, page 7).

As noted in the previous office action, Falck-Pedersen describes replication deficient adenoviruses to be propagated to include those from groups A, B, D E and F while using a cell line that complements the essential gene function of the group C adenoviruses, including Ad 5 (see column 10). Falck-Pedersen describes the functional interaction of the E4 gene product and the essential E1 gene product lead to more fully complement the adenovirus and the

ability to functionally interact is absolutely conserved within a serotype. While there are sufficient differences in the E4 sequences across different subgroups as noted by the Applicant, the E4 regions were clearly known (see reference C02) and the ordinary artisan could readily envisage the invention of Falck-Pedersen in using the E1 and E4 of one serotype while the replication defective virus is from another.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 recites the limitation "replication-defective adenovirus" in claim 7. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that

the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 7, 9-11, 21 and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Falck-Pedersen, Mehtali et al and Fallaux et al (1998) in further view of US Patent 5712136 (Wickham et al). Falck-Pedersen and Mehtali et al have been previously cited.

Falck-Pedersen discloses a method of producing a replication deficient adenovirus in which the virus is deficient in both E1 and E4 functions. The adenovirus is produced in a cell that provides *in trans* the gene functions of the E1 and E4 regions of an adenovirus "not belonging to the same serogroup as the replication deficient adenovirus" (see Abstract). The replication deficient adenoviruses to be propagated as disclosed by Falck-Pedersen include those from groups A, B, D, E and F while using a cell line that complements the essential gene function of the group C adenoviruses, including Ad 5 (see column 10 and Examples 1-8). Further, Falck- Pedersen discloses that the essential gene function of the E4 region are harmful to the host cell and a regulable promoter may be useful so that the gene function of the E4 region can be provided only when the replication deficient adenovirus is in need of the toxic

gene products for its replication. This prior art reference also discloses the following recitation: "The ability to functionally interact appears to be absolutely conserved within a serotype, but less conserved between differing serotypes of a serogroup, and nonconserved between viruses of differing serogroups. Thus, it will be readily appreciated that in some embodiments of the present invention it is preferable for the essential gene products of the E1 and E4 regions of the adenoviral genome to be derived from the same serogroup, and even more preferable for them to be derived from the same serotype" (column 8). Falck-Pedersen reveals the following finding in Example 6: "this example demonstrates that the provision of a gene function of the E4 region of the adenoviral genome in addition to the essential gene functions of the E1 region of the adenoviral genome surprisingly increases the efficiency of complementation of E1 deficient adenoviruses when the E1 gene products provided *in trans* are obtained from an adenovirus of a serogroup different from that of the replication deficient adenovirus" (columns 14-15). The author notes that the foreign gene can be inserted into the E1 region and place under the control of various promoters (column 6). While this reference does not explicitly express an adenovirus of serotype 24, 26 or 36, the teachings do provide that the adenovirus may be subgroup D and it is known in the prior that that this subgroup comprises serotypes 24, 26 and 36 (see Wickman et al, column 6). This reference does not teach the actual placement of the E4 gene (ORF6) into the replication defective adenovirus.

Mehtali et al describe the use of a polynucleotide encoding one or more ORF(s) of the E4 region (see Abstract), including the use of heterologous E4 sequences (co1.4, lines 35-41, col. 7, lines 55-56 and col. 9, lines 35-38) in replication defective adenoviruses "to improve the expression and/or persistence of expression of a recombinant gene in a host cell or organism" (see column 1). A complementation cell line is used to complement the E1 function (see column 10). The gene of interest may be inserted in place of the deleted E1 sequence in an El- adenoviral vector (see column 9). Also, this prior art reference recites the following "the invention describes the use of a polynucleotide encoding one or more ORF(s) of the E4 region of an adenovirus selected from ORF1, ORF2, ORF3, ORF4, ORF3/4, ORF6/7, ORF6 and ORF7 taken individually or in combination, to improve the expression and/or persistence of expression of a gene of interest operably linked to regulatory elements and inserted into an expression vector" (Abstract). Both homologous and heterologous E4 promoters are taught by Mehtali et al (see paragraph 37). Mehtali et al further disclose the following recitation: "In a particularly preferred embodiment the vector into which the polynucleotide comprising the E4ORFs are inserted, is an adenoviral vector, preferably one from which the E4 region has been deleted" (paragraph 41). The following recitation by Mehtali et al reveals the placement of the heterologous E4 region: "it is also possible that the vector is constructed by deleting all E4 sequences, in particular all E4ORFs, and inserting certain E4ORFs from the same or other adenovirus backbones in the adenoviral vector at a location where the E4 region normally resides or at a different location, e.g. in place of the

deleted E1 or E3 region (paragraph 16). Lastly, Mehtali et al teach providing E4ORF *in cis* or *trans* to an E4 deleted vector carrying a transgene (paragraph 14). This reference reveals that impaired transgene expression in E4- deleted adenoviral vectors could be fully restored by the presence and expression of certain E4ORFs and that the E4 region may vary between the different adenovirus strains (column 3). Thus, this reference describes an insertion of heterologous E4ORFs in order to improve the expression and/or persistence of expression of a gene of interest *in cis*.

Fallaux et al (1998) provide an Ad5 E1-complementing cell line, dubbed PER cells. The authors demonstrate that the cells synthesize high levels of the Ad5 E1A and E1B proteins, under the control of the PGK promoter (see Abstract).

Thus, it would have been obvious to one of ordinary skill in the art to combine the teachings above in order to perform the claimed method. One would have been motivated to do so as taught by Falck-Pedersen in the following recitation:

"For many of these applications it is useful to use a replication deficient adenovirus of a particular serotype. The reasons for this are multifold, but include the fact one serotype of adenovirus by definition is not reactive to an adenovirus of another serotype. Therefore, if a mammal, including a human, is exposed to one serotype of adenovirus, it will develop an immune reaction specific for

that strain of adenovirus, but not to distinct strains. Thus, distinct strains can then be used to avoid the humoral and the cellular immune responses specific for other adenoviruses. Moreover, different serotypes of adenoviruses are trophic for distinct cell types. Thus, a replication deficient adenovirus useful in transferring passenger genes to one cell type can be less optimal than a second adenovirus for transfer of that passenger gene to a second cell type. Thus, there is a need for replication deficient adenoviruses of multiple strains. However, if each adenoviral strain requires its own complementing cell, even if that complementing cell were constructed by co-infection with a helper virus, it would be an expensive, tedious, and time consuming process to produce a new complementing cell line for each adenoviral serotype" (see columns 6 and 7). And, by inserting the heterologous Ad 5 E4 region into the replication defective virus of another serotype, the artisan can simply use cells already known to successfully synthesize sufficient levels of Ad 5 E1 gene products such as the PER cells taught by Fallaux et al. There would have been a reasonable expectation of success given the teachings above demonstrate successful methods and products. It is noted that Applicant failed to show any gain of function or surprising results from an *in cis* placement of the heterologous

E4 region. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1 and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Falck-Pedersen, Mehtali et al, Fallaux et al and Megede et al (2000). The teachings of Falck-Pedersen, Mehtali et al and Fallaux et al are applied as they are above. They do not disclose a replication-defective adenovirus comprising a heterologous gene of interest or an HIV-1 antigen.

Megede et al teach that gag is believed to be an important target for the host cell-mediated immune control of the virus during natural infection (see Abstract). It would have been obvious to one of ordinary skill in the art to use the HIV-1 gag as the gene of interest in the method. One would have been motivated to do so in order to express gag proteins for vaccines as disclosed by Megede et al (see Abstract). There would have been a reasonable expectation of success given the gene has been characterized and the underlying techniques are demonstrated to be successful by Falck-Pedersen, Mehtali et al and Fallaux et al. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE HORNING whose telephone

number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michelle Horning/
Examiner, Art Unit 1648

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